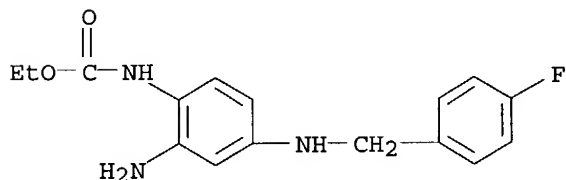


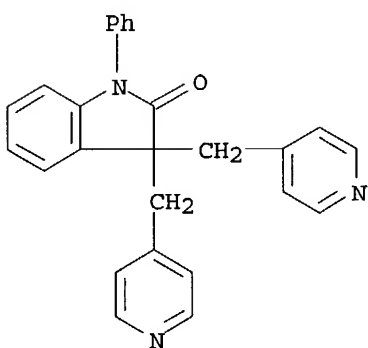
L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 150812-12-7 REGISTRY  
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ester (9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN D 23129  
CN Ethyl [2-amino-4-[[4-(4-fluorophenyl)methyl]amino]phenyl]carbamate  
CN **Retigabine**  
FS 3D CONCORD  
MF C16 H18 F N3 O2  
CI COM  
SR CA  
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA,  
CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMLIST, DDFU, DRUGU, EMBASE,  
IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROMT, RTECS\*, SYNTHLINE,  
TOXCENTER, USAN, USPAT2, USPATFULL  
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59 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 105431-72-9 REGISTRY  
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(CA INDEX NAME)  
OTHER NAMES:  
CN DuP 996  
CN **Linopirdine**  
FS 3D CONCORD  
MF C26 H21 N3 O  
CI COM  
SR CAS Client Services  
LC STN Files: ADISINSIGHT, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,  
CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN, EMBASE,  
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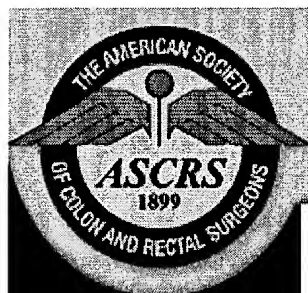
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## FUNCTIONAL BOWEL DISEASE / CONSTIPATION

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### Functional Bowel Disorders

#### Definition

A **functional bowel** disorder is a **functional** gastrointestinal disorder with attributable to the mid or lower gastrointestinal tract. The **functional bowel** include irritable **bowel** syndrome (IBS), **functional** abdominal bloating, **functional** constipation, **functional** diarrhea and unspecified **functional bowel** disorder. The female to male ratio of IBS ranges from 1:1 to 2:1 in the community, except where there is a male predominance. The prevalence of IBS is lower in the elderly. **Functional bowel** diseases can be diagnosed based on established criteria after exclusion of organic causes. The Rome II diagnostic criteria pertaining to the framework to understand, categorize and treat these gastrointestinal disorders. The Rome criteria have also helped to standardize the selection of patients for clinical trials and surveys. They have also allowed patient groups to be selected based on predominant IBS symptom pattern (constipation, diarrhea or bloating), then to evaluate the predicted effect of a particular treatment.(1)

#### Diagnosis

The Rome II diagnostic criteria for IBS include at least 12 weeks or more not be consecutive, in the preceding 12 months of abdominal discomfort

has two out of three features: (1) Relieved with defecation and /or (2) Onset with a change in frequency of stool; and/or (3) Onset associated with a change in appearance of stool. Supportive symptoms of IBS include (a greater than occurrence of) (I) Fewer than three **bowel** movements per week (II) More **bowel** movements per day (III) Hard or lumpy stools (IV) Loose (mushy) stools (V) Straining during a **bowel** movement (VI) Urgency (VII) Feeling incomplete **bowel** movement (VIII) Passing mucous during a **bowel** movement (IX) Abdominal fullness, bloating or swelling. (1)

*Diarrhea-predominant IBS* is associated with one or more of the supportive symptoms II, IV or VI; or two or more of II, IV or VI and none of I or V. *Constipation-predominant IBS* is associated with one or more of the supportive symptoms I, III or V and two or more of II, IV or VI. (1) If diarrhea or constipation are not dominant then the IBS is *probable IBS* if associated with abdominal discomfort or *pain*. (1)

### Evaluation

A limited screen for organic **disease** is indicated to complement a positive IBS based on the Rome II criteria. Screening should include hematology, erythrocyte sedimentation rate, stool examination for occult blood, stool for parasites and gram stain, flexible sigmoidoscopy with biopsy in those with a flexible sigmoidoscopy and air contrast barium enema or colonoscopy in those > 40 with a family history of colon polyps or cancer. (2) A high erythrocyte sedimentation rate, anemia and rectal bleeding are negative predictive factors for the **functional bowel** diseases and should alert the clinician to an alternate **disease** process that needs to be evaluated further.

Intractability in *constipation predominant IBS* can be further investigated with a transit study, anorectal manometry, balloon expulsion test and dynamic perineal manometry. *Diarrhea-predominant IBS* can be further evaluated with a lactulose H<sub>2</sub> breath test, stool osmolality and electrolytes, jejunal aspirate for ova and parasites and anorectal transit. *Pain-predominant IBS* can be further evaluated with abdominal palpation and a small **bowel** series, lactulose H<sub>2</sub> breath test and gastrointestinal manometry.

### Treatment

*Diarrhea-predominant IBS* can be treated with dietary restriction (lactulose, sorbitol), loperamide or diphenoxylate as well as cholestyramine. Tricyclic antidepressants significantly relieve diarrhea and associated pain at least as well as the anticholinergic effect. Calcium channel blockers may be used as second-line treatment. 5HT<sub>3</sub> (alosetron) and 5HT<sub>4</sub> receptor antagonists may also be used for controlling diarrhea-predominant IBS. (2)

Patients with *pain-predominant IBS* may benefit from treatment with antidepressants with or without anxiolytics and avoidance of gas forming foods. Smooth muscle relaxants such as mebeverine, octylonium and cimetropium are worthy of a clinical trial in view of a mean response of pain in a meta-analysis of 68% compared to placebo. (2) New treatment modalities in clinical trial evaluation include the 5HT<sub>2</sub> antagonist fedotozine. (1,2)

*Constipation-predominant IBS* has been shown to improve significantly with treatment.

agents in clinical trials. Osmotic laxatives like milk of magnesia or lactulose softeners may be added to the regimen if bulk agents alone are not sufficient. Anticholinergics may cause or aggravate constipation through the anticholinergic effect and should, therefore, be avoided in the subgroup with pain and constipation-predominant IBS. (2) Currently, phase III clinical trials are evaluating the effectiveness of 5-HT<sub>4</sub> receptor agonists for treatment of chronic constipation, including constipation-predominant IBS.

Other potential therapies for IBS include selective serotonin re-uptake inhibitors, antimuscarinic agents, alpha-2 adrenergic agents, somatostatin analogs and antagonists. (2). The somatostatin analog Octreotide reduces orocecal transit time and increases colonic visceral sensory threshold in IBS, but has limited clinical utility in view of its parenteral mode of administration. (1)

## Constipation

### Definition

Constipation is a symptom of many diseases and is a collective term used when stools are either too hard, too infrequent or too difficult to pass. Constipation is defined by the presence of two or more of the following symptoms over a three-month period when the patient is not taking laxatives: (a) straining at defecation >25% of the time, (b) lumpy and/or hard stools > 25% of the times, (c) sensation of incomplete evacuation >25% of the time and (d) two or fewer bowel movements per week.

### Historical Perspective

In the early part of the 20th century, Sir William Arbuthnot Lane advocated ileorectal anastomosis for the treatment of a variety of disorders, including chronic constipation. The condition referred to then as chronic intestinal stasis or Arbuthnot Lane's disease. The majority of colectomies performed by Lane were for chronic constipation. 93 patients treated for constipation by colectomy or bypass. Only eight were men and two-thirds of the women were aged 35 or under. (5)

### Etiology

It is difficult to determine the underlying etiology of constipation in Lane's patients. However, no evidence of megacolon was present in any of the 85 women with chronic constipation. It is likely, therefore, that many of the women operated on had a normal sized colon and that they were suffering from idiopathic slow-transit constipation. Associations between constipation and disorders such as poor circulation, breast disease, infertility, estrogen deficiency and ovarian cysts have been described. (4,5) Other studies have associated chronic constipation with the use of laxatives. (5) Although slow-transit constipation without megarectum affects both men and women in almost equal proportion, slow-transit constipation with megarectum affects males and females in equal proportion. (6-8) Table 1 summarizes the most common causes of constipation.

**Table 1 Causes of Constipation**

|           |  |
|-----------|--|
| Endocrine | insulin-dependent diabetes mellitus, hypopituitarism |
|-----------|--|

|   |   |
|---|---|
|   | hypothyroidism, hypercalcemia, pseudo-hypoparathyroidism, pheochromocytoma, glucagonoma, pregnancy, steroid hormones in luteal and follicular phases of menstrual cycle   |
| Metabolic disorders   | porphyria, uremia, hypokalemia, amyloid neuropathy  |
| Neurologic disorders  | Parkinson's <b>disease</b> , cerebral tumors, cerebrovascular accidents, multiple sclerosis, scleroderma, meningocele, aganglionosis, Chagas <b>disease</b> , hyperganglionic autonomic neuropathy, spinal cord injury, major depression, anxiety, obsessional personality disorders  |
| Surgery resulting in localized damage to autonomic nervous plexus | pelvic surgery (cystectomy, rectopexy, hysterectomy)  |
| Pharmacologic agents  | Opioids, anticholinergics, anticonvulsants, antacids (aluminum containing), anti-Parkinsonian agents, antihypertensive agents, chronic stimulant laxatives (senna, cascara, anthraquinones, bisacodyl), mucolytics, oxidase inhibitors, tricyclics, phenothiazines, alkaloids (vincristine), heavy metal poisoning (lead, mercury, phosphorus, iron, oral contraceptives, muscle relaxants) |
| Obstructive <b>bowel</b> diseases                                 | Endometriosis, carcinoma, volvulus, hernia, benign strictures, pseudo-obstruction, polyps, adhesions  |
| <b>Functional</b>   | Irritable <b>bowel</b> syndrome, anismus, sedentary-lifestyle patients  |
| Dietary   | Inadequate fiber or fluid intake  |
| Primary or idiopathic   | No specific underlying condition identified   |

### Diagnostic Modalities

Preliminary evaluation of constipated patients starts with a thorough history and physical exam in order to identify changes in lifestyle, medication regime, and bowel status. Patients undergoing workup of constipation should have a *flexible sigmoidoscopy* and *barium enema* for heme-negative stools or a *colonoscopy* for heme-positive stools. Such studies enable exclusion of malignancy and other anatomic abnormalities of the lower gastrointestinal tract. Laboratory bloodwork should include thyroid function tests, ionized calcium and glucose in order to evaluate for hypothyroidism, hypercalcemia and diabetes. Constipation refractory to lifestyle modifications benefits from manometric documentation of the *anal inhibitory reflex* (RAIR). RAIR allows differentiation between idiopathic constipation and aganglionosis in whom the reflex is absent. *Anorectal manometry* also allows documentation of anal sphincter pressures to rule out hypertonia and associated obstruction. *Dynamic proctography* provides cineradiographic evidence of anatomic pathology, such as rectoceles, enteroceles and rectal prolapse, that may contribute to outlet obstruction and difficulty with **bowel** movements. *Intestinal transit studies* allow objective measurement of constipation. Colon transit analysis enables determination of segmental and total colon transits and thereby identifies normal and slow colonic transit.

### Anatomy and Physiology

The cause of slow whole gut transit in patients with a normal-sized colon rectoanal inhibitory reflex is not completely understood. Constipation syndrome also be associated with a disorder of the striated muscle of the pelvic floor contracts inappropriately with attempted defecation (anismus or paradoxical puborectalis) rather than relax as in normal individuals.(8) The epidemiological constipation study in the United States noted an overall prevalence of 14.7%. Prevalence according to subtype was 4.6% for **functional**, 2.1% for outlet and 3.4% for IBS-outlet associated constipation.(9)

Studies of colonic motility have shown that patients with slow transit constipation have colonic hypersegmentation and that many have little spontaneous contraction or response to topical stimulation with bisacodyl.(10) This latter finding suggests possible abnormality of the myenteric plexus. Peptide containing nerves appear to be normal, but there may be abnormalities in the morphology of the myenteric plexus.(11)

Failure of normal gastrin, motilin and pancreatic polypeptide release has been documented in patients with severe constipation, although this may represent a secondary phenomenon.(12,13) Measurement of sex hormones have shown abnormalities, such as hyperprolactinemia which may be related to other reproductive symptoms common in these patients.(14) In addition, coworkers in 1991 noted a constant reduction in estradiol, cortisol and testosterone during the luteal and follicular phases as well as reduced progesterone and 17 hydroxyprogesterone, androstenedione and dehydroepiandrosterone in the luteal phase of women with severe chronic constipation.(15)

### Treatment

In most cases, constipation can be treated with dietary manipulation, stimulant laxatives, and enemas. However, there is a group of patients for whom medical management is unsatisfactory and in whom stimulant laxatives quickly lose their effect suggesting myenteric plexus damage.

One approach to the therapy of chronic constipation consists of stimulating physiological as possible, intestinal motility (*Table 2*). In the colon, high amplitude propagated contractions occur a few times a day, especially right after and before meals. These so called mass movements or giant migrating contractions provide the main propulsive force to fast colonic propulsion and often are associated with the urge to defecate. In idiopathic chronic constipation, the number and duration of mass movements is smaller than in healthy subjects (16).

A new chemical class (*benzofurans*) has been shown to specifically induce to stimulate proximal colonic motility in humans. These agents also stimulate pyloro-duodenal motility and accelerate delayed gastric emptying in the rat. The effect is mediated by selective stimulation of serotonin 5HT4 receptors which facilitate cholinergic as well as non-cholinergic excitatory neurotransmission and enhance the enterokinetic effect. This class of agents is currently being studied in clinical trials for treatment of chronic constipation.(17)

*Surgical treatment* is undertaken in patients with chronic idiopathic constipation with great reluctance and only because patients are greatly disabled in view of medical management. The severity of constipation in these individuals that colectomy is unusual. Local sphincter surgery or segmental colon resection benefit patients with slow transit constipation. Internal sphincterotomy may benefit a select group of individuals with hypertonic anal sphincter and impaired or not alleviate symptoms from paradoxical puborectalis activity. Sigmoid colectomy can be performed for recurrent sigmoid volvulus. *However, total abdominal colectomy with ileorectal anastomosis* gives the best chance of a good **functional** result with severe slow transit constipation refractory to medical management (18). Following total abdominal colectomy with ileorectal anastomosis the life can be transformed from an existence dominated by the absence of normal bowel function and abdominal discomfort and the use of laxatives, to normality in approximately 80%. Most patients report a return of the urge to defecate after colectomy. (3, 11) The selection of surgical intervention for constipation depends on careful consideration of treatment of slow colonic transit and/or any associated pelvic floor pathology including enteroceles, rectoceles and prolapse. Surgical management of carefully selected patients with slow transit constipation and concomitant pelvic floor hernia has been shown to yield satisfactory results in 89%. (19)

Although serious immediate postoperative complications are rare following total abdominal colectomy with ileorectal anastomosis, prolonged ileus tends to be a problem. In addition, a high incidence of small bowel obstruction has been noted following total abdominal colectomy for constipation. Diarrhea and fecal incontinence may also occur following total colectomy. (5)

**Table 2 Treatment Options for Chronic Idiopathic Constipation**

|   |  |
|---|--|
| Underlying pathology                    | Correct causative underlying conditions and eliminate unnecessary medications if possible  |
| Activity level                          | Increase mobility  |
| Dietary manipulations                   | High fiber intake (20-30 g / day) Konsyl(r) / Metamucil(r) 1 tbs. PO BID Increase non-caffeinated fluids (8-10 8 oz glasses / day) |
| Stool softeners                         | Sodium docusate 100 mg PO BID<br>Mineral oil 1 oz PO BID   |
| Stimulant laxatives                     | Pericolace(r) 1 PO QD<br>Dulcolax(r) 5-15 mg PO if no BM for 3 or more consecutive days  |
| Prokinetic agents                       | Benzofuran PO QD (clinical trial)  |
| Enemas                                  | Fleets(r) enema if no BM for 3 days  |
| Osmotic agents                          | Milk of Magnesia 30-60 PO QD<br>Lactulose 30 ml PO QD-BID<br>Polyethyleneglycol (PEG) 10-20 oz PO QD<br>Miralax(r) 17 gm PO QD     |
| Psychological support and evaluation as | Counseling, MMPI   |



|                       |  |
|-----------------------|--|
| indicated             |  |
| Surgical intervention | Subtotal colectomy with ileorectal anastomosis<br>Subtotal colectomy with ileostomy<br>Diverting ileostomy |

### Conclusion

**Functional bowel** diseases can be diagnosed based on the Rome II criteria. Subgrouping of IBS into predominantly diarrhea, constipation or pain allows stratification of IBS based on symptomatology also facilitates establishment of modalities for specific IBS types. Idiopathic slow transit constipation represents a complex disorder. For the patients who develop severe and disabling idiopathic constipation, unresponsive to dietary modification or drugs, colectomy with ileorectal anastomosis can offer great benefit. Careful physiologic and anatomic evaluation is required for refractory idiopathic constipation and any associated pelvic outlet pathology to tailor the surgical operation to meet the needs of the patient.

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